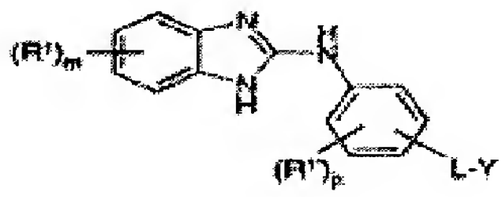
WO 05/019216 Translation

Patent claims

1. Compounds of structure I



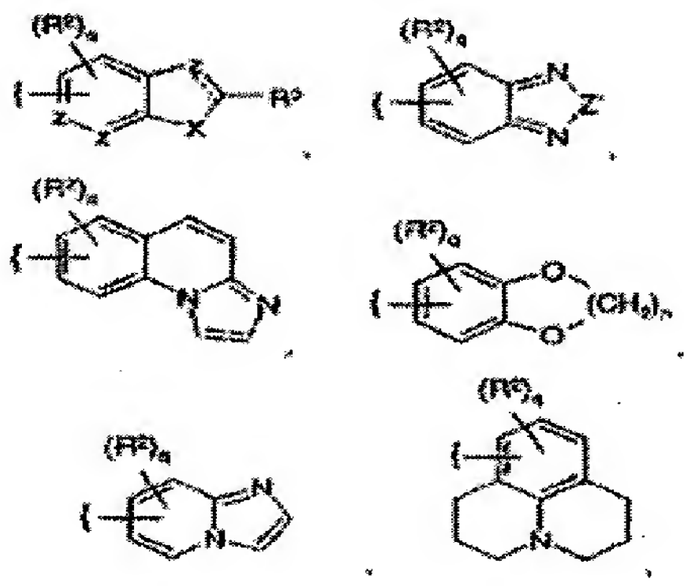
I

where

R^1, $R^{1'}$ independently of each other, are Hal, A, OH, OA, CN, COOH, COOA, $CONH_2$, CONHA or $CONA_2$,

L is CH_2, CH_2CH_2, O, S, SO, SO_2, NH, NA, C=O or CHOH,

Y is a heterocycle selected from the list



R^2 is Hal, A, OH, OA, CN, COOH, COOA, $CONH_2$, CONHA or $CONA_2$,

R^3 is H, A, NH_2, COOH, COOA, $CONH_2$, CONHA, $CONA_2$ or NHCOOA,

X is S, O, NH, NA or CH_2,

Z is -CH=, CH_2, NH, -N= or C=O,

Z' is S or O,

A is an unbranched, branched or cyclic alkyl with 1-10 C atoms, where 1-7 H atoms may be replaced by F and/or chlorine,

Hal is F, Cl, Br or I,

m, p, q independently of each other, are 0, 1, 2, 3 or 4

n is 1, 2 or 3,

and also their pharmaceutical usable derivatives, solvates, salts and stereoisomers, including mixtures of these in all proportions.

2. Compounds as per Claim 1, where

R^1 is A or Hal,

m is 1, 2 or 3,

and also their pharmaceutical usable derivatives, solvates, salts and stereoisomers, including mixtures of these in all proportions.

3. Compounds as per Claim 1 or 2, where

R^1 is CF_3, F or Br,

m is 1, 2 or 3,

and also their pharmaceutical usable derivatives, solvates, salts and stereoisomers, including mixtures of these in all proportions.

4. Compounds as per one or several of Claims 1-3, where

R^1 is Hal or A,

p is 0 or 1,

and also their pharmaceutical usable derivatives, solvates, salts and stereoisomers, including mixtures of these in all proportions.

5. Compounds as per one or several of Claims 1-4, where

L is O, S or CH_2

and also their pharmaceutical usable derivatives, solvates, salts and stereoisomers, including mixtures of these in all proportions.

6. Compounds as per one or several of Claims 1-5, where

R^2 is A, COOA or $CONH_2$,

q is 0, 1 or 2

and also their pharmaceutical usable derivatives, solvates, salts and stereoisomers, including mixtures of these in all proportions.

7. Compounds as per one or several of Claims 1-6, where

R^3 is H, NH_2 or COOA

and also their pharmaceutical usable derivatives, solvates, salts and stereoisomers, including mixtures of these in all proportions.

8. Compounds as per one or several of Claims 1-7, where

R^1 is A or Hal,

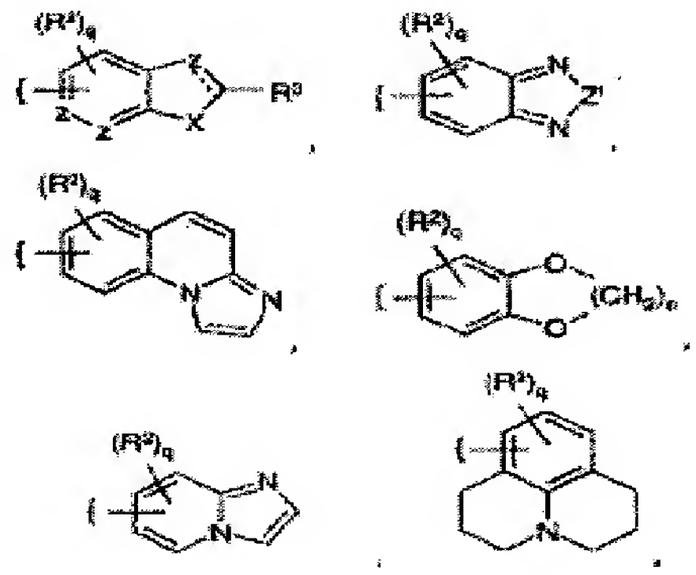
m is 1, 2 or 3,

$R^{1'}$ is Hal or A,

p is 0 or 1,

L is O, S or CH_2,

Y is a heterocycle selected from the list



R^2 is A, COOA or $CONH_2$,

q is 0, 1 or 2,

R^3 is H, NH_2 or COOA,

n is 1, 2 or 3,

and also their pharmaceutical usable derivatives, solvates, salts and stereoisomers, including mixtures of these in all proportions.

9. Compounds as per claim 1, selected from the group

[4-(benzo(1,2,5)thiadiazole-5-yloxy)-phenyl]-(4-bromo-6-trifluoromethyl-1*H*-benzimidazole-2-yl)-amine,

[4-(benzo(1,2,5)thiadiazole-5-yloxy)-phenyl]-(4-chloro-6-trifluoromethyl-1*H*-benzimidazole-2-yl)-amine,

[4-(benzo[1,3]dioxol-5-yloxy)-phenyl]-(4-chloro-6-trifluoromethyl-1*H*-benzimidazole-2-yl)-amine,

[4-(benzo[1,2,5]thiadiazole-5-yloxy)-phenyl]-(4-bromo-6-trifluoromethyl-1*H*-benzimidazole-2-yl)-amine,

(4-bromo-6-trifluoromethyl-1*H*-benzimidazole-2-yl)-[4-(imidazo[1,2-a]quinoline-9-yloxy)-phenyl]-amine,

(4-chloro-6-trifluoromethyl-1*H*-benzimidazole-2-yl)-[4-(imidazo[1,2-a]quinoline-9-yloxy)-phenyl]-amine,

(7-bromo-5-trifluoromethyl-1*H*-benzimidazole-2-yl)-[4-(2-butyl-imidazo[4,5-b]pyridine-4-ylmethyl]-phenyl)-amine,

[4-(2-butyl-imidazo[4,5-bipyridine-4-ylmethyl)-phenyl]-(7-chloro-5-trifluoromethyl-1*H*-benzimidazole-2-yl)-amine,

(4-chloro-6-trifluoromethyl-1*H*-benzimidazole-2-yl)-[4-(1*H*-indole-6-yloxy)-phenyl]-amine,

[4-(benzo[1,2,5]thiadiazole-4-yloxy)-phenyl]-(4-chloro-6-trifluoromethyl-1*H*-benzimidazole-2-yl)-amine,

(4-bromo-6-trifluoromethyl-1*H*-benzimidazole-2-yl)-[4-(1*H*-indole-5-yloxy)-phenyl]-amine,

(4-bromo-6-trifluoromethyl-1*H*-benzimidazole-2-yl)-[4-(1*H*-indole-5-yloxy)-phenyl]-amine,

(4-chloro-6-trifluoromethyl-1*H*-benzimidazole-2-yl)-[4-(1*H*-indole-5-yloxy)-phenyl]-amine,

(4-bromo-6-trifluoromethyl-1*H*-benzimidazole-2-yl)-[4-(1*H*-indole-6-yloxy)-phenyl]-amine,

(7-bromo-5-trifluoromethyl-1*H*-benzimidazole-2-yl)-(4-imidazole[4,5-b]pyridine-3-ylmethyl-phenyl]-amine,

(7-chloro-5-trifluoromethyl-1*H*-benzimidazole-2-yl)-(4-imidazole[4,5-b]pyridine-3-ylmethyl-phenyl]-amine,

(7-bromo-5-trifluoromethyl-1*H*-benzimidazole-2-yl)-[4-(2,3,6,7-tetrahydro-1*H*,5*H*-pyrido[3,2,1-ij]quinoline-8-yloxy)-phenyl]-amine,

(7-chloro-5-trifluoromethyl-1*H*-benzimidazole-2-yl)-[4-(2,3,6,7-tetrahydro-1*H*,5*H*-pyrido[3,2,1-ij]quinoline-8-yloxy)-phenyl]-amine

5-[4-(7-bromo-5-trifluoromethyl-1*H*-benzimidazole-2-ylamino)-phenoxy]-1*H*-indole-2-carboxylic acid ethylester,

5-[4-(7-chloro-5-trifluoromethyl-1*H*-benzimidazole-2-ylamino)-phenoxy]-1*H*-indole-2-carboxylic acid ethylester,

7-[4-(7-bromo-5-trifluoromethyl-1*H*-benzimidazole-2-ylamino)-phenoxy]-benzofuran-2-carboxylic acid methylester,

7-[4-(7-chloro-5-trifluoromethyl-1*H*-benzimidazole-2-ylamino)-phenoxy]-benzofuran-2-carboxylic acid methylester,

[4-(benzo[1,2,5]oxadiazole-5-yloxy)-phenyl]-(4-bromo-6-trifluoromethyl-1*H*-benzimidazole-2-yl)-amine,

7-[4-(4-bromo-6-trifluoromethyl-1*H*-benzimidazole-2-ylamino)-phenoxy]-benzofuran-2-carboxylic acid amide,

7-[4-(4-chloro-6-trifluoromethyl-1*H*-benzimidazole-2-ylamino)-phenoxy]-benzofuran-2-carboxylic acid amide,

[4-(benzo[1,2,5]oxadiazole-5-yloxy)-phenyl]-(4-fluoro-6-trifluoromethyl-1*H*-benzimidazole-2-yl)-amine,

[4-(benzo[1,2,5]thiadiazole-4-yloxy)-phenyl]-(4-fluoro-6-trifluoromethyl-1*H*-benzimidazole-2-yl)-amine,

[4-(benzo[1,3]dioxol-5-yloxy)-phenyl]-(4-bromo-6-trifluoromethyl-1*H*-benzimidazole-2-yl)-amine,

(4-bromo-6-trifluoromethyl-1*H*-benzimidazole-2-yl)-[4-(3-methyl-3*H*-imidazo[4,5-c]pyridine-4-ylsulfanyl)-phenyl]-amine,

6-[4-(7-chloro-5-trifluoromethyl-1*H*-benzimidazole-2-ylamino)-phenoxy]-4,7-dimethyl-benzothiazole-2-ylamine,

(7-chloro-5-trifluoromethyl-1*H*-benzimidazole-2-yl)-[4-imidazo[1,2-a]pyridine-8-yloxy)-phenyl]-amine,

[4-(benzo[1,2,5]thiadiazole-5-yloxy)-phenyl]-(4-fluoro-6-trifluoromethyl-1*H*-benzimidazole-2-yl)-amine,

[4-(benzo[1,2,5]thiadiazole-5-yloxy)-phenyl]-(4-6-difluoro-1*H*-benzimidazole-2-yl)-amine,

(4-bromo-6-trifluoromethyl-1*H*-benzimidazole-2-yl)-[2-(2,3-dihydrobenzo[1,4]dioxine-6-yloxy)-phenyl]-amine,

[4-(benzo[1,2,5]thiadiazole-5-yloxy)-phenyl]-(4-5-difluoro-1*H*-benzimidazole-2-yl)-amine,

[4-(benzo[1,2,5]thiadiazole-5-yloxy)-phenyl]-(5-6-difluoro-1*H*-benzimidazole-2-yl)-amine,

(7-chloro-5-trifluoromethyl-1*H*-benzimidazole-2-yl)-[2-(2,3-dihydrobenzo[1,4]dioxine-6-yloxy)-phenyl]-amine,

6-[4-(7-chloro-5-trifluoromethyl-1*H*-benzimidazole-2-ylamino)-phenoxy]-benzothiazole-2-ylamine,

(6,7-difluoro-1*H*-benzimidazole-2-yl)-[4-(3-methyl-3*H*-imidazo[4,5-c]pyridine-4-ylsulfanyl)-phenyl]-amine,

(4-bromo-6-trifluoromethyl-1*H*-benzimidazole-2-yl)-[4-(2-methyl-benzothiazole-5-yloxy)-phenyl]-amine,

(4-chloro-6-trifluoromethyl-1*H*-benzimidazole-2-yl)-[4-(2-methyl-benzothiazole-5-yloxy)-phenyl]-amine,

[2-(benzo[1,2,5]thiadiazole-5-yloxy)-phenyl]-(4-bromo-6-trifluoromethyl-1*H*-benzimidazole-2-yl)-amine,

(7-bromo-5-trifluoromethyl-1*H*-benzimidazole-2-yl)-[4-(imidazo[1,2-a]pryidine-8-yloxy)-phenyl]-amine,

[2-(benzo[1,2,5]thiadiazole-5-yloxy)-phenyl]-(7-chloro-5-trifluoromethyl-1*H*-benzimidazole-2-yl)-amine,

(4-bromo-6-trifluoromethyl-1*H*-benzimidazole-2-yl)-[4-(2,3-dihydrobenzo[1,4]dioxine-6-yloxy)-phenyl]-amine,

(7-chloro-5-trifluoromethyl-1*H*-benzimidazole-2-yl)-[4-(2,3-dihydrobenzo[1,4]dioxine-6-yloxy)-phenyl]-amine,

[2-(benzo[1,2,5]thiadiazole-4-yloxy)-phenyl]-(4-bromo-6-trifluoromethyl-1*H*-benzimidazole-2-yl)-amine,

[2-(benzo[1,2,5]thiadiazole-4-yloxy)-phenyl]-(7-chloro-5-trifluoromethyl-1*H*-benzimidazole-2-yl)-amine,

(4-bromo-6-trifluoromethyl-1*H*-benzimidazole-2-yl)-[4-(1-methyl-1*H*-imidazo[4,5-c]pyridine-4-ylsulfanyl)-phenyl]-amine,

[4-(benzo[1,2,5]thiadiazole-5-yloxy)-3-methyl-phenyl]-(7-bromo-5-trifluoromethyl-1*H*-benzimidazole-2-yl)-amine,

[4-(benzo[1,2,5]thiadiazole-5-yloxy)-3-methyl-phenyl]-(7-chloro-5-trifluoromethyl-1*H*-benzimidazole-2-yl)-amine

[4-(benzo[1,2,5]thiadiazole-5-yloxy)-2-methyl-phenyl]-(7-bromo-5-trifluoromethyl-1*H*-benzimidazole-2-yl)-amine

[4-(benzo[1,2,5]thiadiazole-5-yloxy)-2-methyl-phenyl]-(7-chloro-5-trifluoromethyl-1*H*-benzimidazole-2-yl)-amine,

(4-bromo-6-trifluoromethyl-1*H*-benzimidazole-2-yl)-[4-(2,3 dihydro-benzo[1,4]dioxine-5-yloxy)-phenyl]-amine,

(4-chloro-6-trifluoromethyl-1*H*-benzimidazole-2-yl)-[4-(2,3 dihydro-benzo[1,4]dioxine-5-yloxy)-phenyl]-amine,

[4-(benzo[1,3]dioxol-4-yloxy)-phenyl]-(4-bromo-6-trifluoromethyl-1*H*-benzimidazole-2-yl)-amine,

[4-(benzo[1,3]dioxol-4-yloxy)-phenyl]-(4-chloro-6-trifluoromethyl-1*H*-benzimidazole-2-yl)-amine,

[4-(benzo[1,3]dioxol-5-yloxy)-phenyl]-(4,5-difluoro-1*H*-benzimidazole-2-yl)-amine,

[4-(benzo[1,3]dioxol-5-yloxy)-phenyl]-(5-fluoro-1*H*-benzimidazole-2-yl)-amine,

[4-(benzo[1,3]dioxol-5-yloxy)-phenyl]-(4,6-difluoro-1*H*-benzimidazole-2-yl)-amine,

[4-(benzo[1,2,5]thiadiazole-5-yloxy)-phenyl]-(5-fluoro-1*H*-benzimidazole-2-yl)-amine,

[4-(benzo[1,2,5]thiadiazole-5-yloxy)-phenyl]-(4,5,6-trifluoro-1*H*-benzimidazole-2-yl)-amine,

(6-chloro-4-trifluoromethyl-1*H*-benzimidazole-2-yl)-[2-(2,3 dihydro-benzo[1,4]dioxine-6-yloxy)-phenyl]-amine,

[4-(benzo[1,2,5]thiadiazole-5-ylsulfanyl)-phenyl]-(4-bromo-6-trifluoromethyl-1*H*-benzimidazole-2-yl)-amine,

[4-(benzo[1,2,5]thiadiazole-5-ylsulfanyl)-phenyl]-(4-chloro-6-trifluoromethyl-1*H*-benzimidazole-2-yl)-amine,

(4-bromo-6-trifluoromethyl-1*H*-benzimidazole-2-yl)-[4-(indan-5-yloxy)-phenyl]-amine,

5-[4-(6-fluoro-1*H*-benzimidazole-2-ylamino)-phenoxy]-indan-1-one,

[4-(benzo[1,2,5]thiadiazole-5-yloxy)-3-fluoro-phenyl]-(7-bromo-5-trifluoromethyl-1*H*-benzimidazole-2-yl)-amine,

[4-(benzo[1,2,5]thiadiazole-5-yloxy)-3-fluoro-phenyl]-(7-chloro-5-trifluoromethyl-1*H*-benzimidazole-2-yl)-amine,

(6,7-difluoro-1*H*-benzimidazole-2-yl)-[4-(indan-5-yloxy)-phenyl]-amine,

(6-fluoro-1*H*-benzimidazole-2-yl)-[4-(indan-5-yloxy)-phenyl]-amine,

[4-(indan-5-yloxy)-phenyl]-(5,6,7-trifluoro-1*H*-benzimidazole-2-yl)-amine,

(5,7-difluoro-1*H*-benzimidazole-2-yl)-[4-(indan-5-yloxy)-phenyl]-amine,

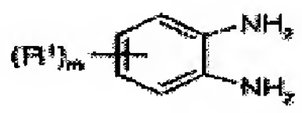
5-[4-(4-bromo-6-trifluoromethyl-1*H*-benzimidazole-2-ylamino)-phenoxy]-benzofuran-2-carboxylic acid ethylester,

5-[4-(4-chloro-6-trifluoromethyl-1*H*-benzimidazole-2-ylamino)-phenoxy]-benzofuran-2-carboxylic acid ethylester,

and also their pharmaceutical usable derivatives, solvates, salts and stereoisomers, including mixtures of these in all proportions.

10. The method for producing compounds of structure I as per claims 1-9 and their pharmaceutical usable derivatives, solvates, salts and stereoisomers is characterised by the reaction between

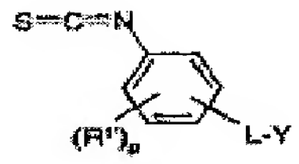
a compound of structure II



II

where R^1 and m are as described in claim 1,

with a compound of structure III



III

where $R^{1'}$, L, Y and p are as described in claim 1,

and/or a base or acid of structure I converted into one of its salts.

11. Medicinal products containing at least one compound as per claim 1 and/or its pharmaceutical usable derivatives, solvates, salts and stereoisomers, including mixtures of them in all proportions and also carrier and/or accessory substances if applicable.

12. Use of compounds as per claim 1 and their pharmaceutical usable derivatives, solvates, salts and stereoisomers, including mixtures of them in all proportions, to produce a medicinal product to treat diseases where the inhibition, regulation and/or modulation of kinase signal transduction plays a role.

13. Use as per claim 12, with kinases selected from the group of tryosine kinases and raf kinases.

14. Use as per claim 13, using the receptor tyrosine kinase Tie2.

15. Use as per claim 12 of compounds as per claim 1 and their pharmaceutical usable derivatives, solvates, salts and stereoisomers, including mixtures of them in all proportions, to produce a medicinal product to treat diseases that are influenced by inhibition of tyrosine kinases by the compounds as per claim 1.

16. Use as per claim 15, to produce a medicinal product to treat diseases that are influenced by inhibition of Tie2 by compounds as per claim 1.

17. Use as per claim 15 or 16, when the disease to be treated is a solid tumour.

18. Use as per claim 17, when the solid tumour is one of the following group: brain tumour, tumour of the urogenital tract, tumour of the lymphatic system, stomach tumour, tumour of the larynx and lung tumour.

19. Use as per claim 17, when the solid tumour is one of the following group: monocytic leukaemia, pulmonary adenocarcinoma, small-cell lung cancer, pancreatic cancer, glioblastoma and breast cancer.

20. Use as per claim 15 or 16, to treat a disease in which angiogenesis plays a role.

21. Use as per claim 20, when the disease is a disease of the eyes.

22. Use as per claim 15 or 16, to treat retinal vascularisation, diabetic retinopathy, age-related macular degeneration and/or inflammatory diseases.

23. Use as per claim 22, when the inflammatory disease is one of the following group: rheumatoid arthritis, psoriasis, contact dermatitis and delayed hypersensitivity reaction.

24. Use as per claim 15 or 16, to treat bone pathologies when the bone pathology is one of the following group: osteosarcoma, osteoarthritis and rickets.

25. Medicinal products containing at least one compound as per claim 1 and/or its pharmaceutical usable derivatives, solvates, salts and stereoisomers, including mixtures of them in all proportions, and at least one other active ingredient.

26. Set (kit) consisting of separate packs of

(a) an effective quantity of a compound as per claim 1 and/or its pharmaceutical usable derivatives, solvates, salts and stereoisomers, including mixtures of them in all proportions and

(b) an effective quantity of another active ingredient.

27. Use of compounds as per claim 1 and/or their physiologically safe salts and solvates, to produce a medicinal product to treat solid tumours, with administration of a therapeutically active quantity of a compound as per claim 1 combined with a compound from group: 1) oestrogen receptor modulators, 2) androgen receptor modulators, 3) retinold receptor modulators, 4) cytotoxics, 5) antiproliferative agents, 6) prenyl-protein transferase inhibitors, 7) HMG-CoA reductase inhibitors, 8) HIV protease inhibitors, 9) reverse transcriptase inhibitors and 10) other angiogenesis inhibitors.

28. Use of compounds as per claim 1 and/or their physiologically safe salts and solvates, to produce a medicinal product to treat solid tumours, with administration of a therapeutically active quantity of a compound as per claim 1 combined with radiotherapy and a compound from group: 1) oestrogen receptor modulators, 2) androgen receptor modulators, 3) retinold receptor modulators, 4) cytotoxics, 5) antiproliferative agents, 6) prenyl-protein transferase inhibitors, 7) HMG CoA reductase inhibitors, 8) HIV protease inhibitors, 9) reverse transcriptase inhibitors and 10) other angiogenesis inhibitors.

29. Use as per claim 12, 13 or 14, to produce a medicinal product to treat diseases that are based on a disturbed Tie2 activity, with administration of a therapeutically active quantity of a compound as per claim 1 combined with a growth factor receptor inhibitor.

30. Use as per claim 12 or 13 of compounds as per claim 1 and their pharmaceutically usable derivatives, solvates, salts and stereoisomers, including mixtures of them in all proportions, to produce a medicinal product to treat diseases that are caused, transmitted and/or spread by Raf kinases.

31. Use as per claim 30, with selection of Raf kinases from the group consisting of A-Raf, B-Raf and Raf-1.

32. Use as per claim 30, with selection of diseases from the group of hyperproliferative and non-hyperproliferative diseases.

33. Use as per claim 30 or 32, when the disease is cancer.

34. Use as per claim 30 or 32, when the disease is not cancerous.

35. Use as per claim 30, 32, or 34 when non-cancerous diseases are selected from the group including psoriasis, arthritis, inflammations, endometriosis, cicatrisation, benign prostate hyperplasia, immunological diseases, autoimmune diseases and diseases caused by a weakened immune system.

36. Use as one of claims 30, 32, or 33, when diseases are selected from the group including brain cancer, lung cancer, squamous cell carcinoma, bladder cancer, stomach cancer, pancreatic cancer, liver cancer, kidney cancer, colorectal cancer, breast cancer, head cancer, neck cancer, oesophageal cancer, gynaecological cancer, thyroid gland cancer, lymphoma, chronic leukaemia and acute leukaemia.